PATENT APPLICATION

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicants: Alice C. MARTINO et al

For: TABLET FORMULATION

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Assistant Commissioner for Patents
Washington, DC 20231

DECLARATION UNDER 37 CFR 1.132

I, Alice C. Martino, declare:

THAT, I received a B.S. degree in Pharmacy from Purdue University in 1980;

THAT, I received a Ph.D. degree in Pharmaceutics from The University of Iowa in 1987;

THAT, I worked at G.D. Searle as an Industrial Pharmacist prior to graduate school from 1980 to 1982;

THAT, I worked at Burroughs Wellcome as a Pharmacy Intern in 1979;

THAT, I worked at Oquawka Professional Pharmacy as a Pharmacist from 1983 to 1986;

THAT, I worked at Walgreens as a Pharmacist and Pharmacy Intern from 1981 to 1982 and 1976 to 1977;

THAT, I worked at Keefer's Pharmacy as a Pharmacy Intern from 1976-1979;

THAT, I joined The Upjohn Company in 1987 as a Research Scientist;

THAT, I am the author or co-author of about nine external scientific publications, about three of which deal with delavirdine (RESCRIPTOR Tablet) formulation and product development;

THAT, I am the inventor or co-inventor of about nine U.S. Patent applications and one U.S. Patent;

THAT, my present position with Pfizer is Principal Research Scientist and my daily duties and responsibilities include design and execution of pharmaceutical formulation development from inception to product launch, including novel exploratory formulations, formulation advisor, leader of a formulation team and leader of a pharmaceutical sciences project team;

THAT, being so qualified the declarant further states;

THAT, I am a co-inventor of the above-identified patent application.

MICROCRYSTALLINE CELLULOSE IS NOT A POLYMERIC BINDER AS THAT TERM IS USED IN THE ABOVE-IDENTIFIED APPLICATION

THAT, microcrystalline cellulose (MCC) functions as a tablet diluent and is not truly a tablet binder. At least, not in the commonly used sense of the word, i.e., to bind together other key materials in the tablet especially the drug and other excipients which otherwise would not exhibit sufficient bond to form a manufacturable tablet. While it is true that MCC itself exhibits self-binding-properties and can accommodate other excipients in this mix and yet form a manufacturable tablet, this is typically the case only if those excipients/drugs contain either a) another material already acting as binder itself or b) if those materials are sufficiently low enough in concentration such that properties of the MCC can override ie that an actual binder is not needed;

THAT, from the Handbook of Drug Excipients, 3rd Ed, 2000: under the delineated item #6 called Functional Category, the following descriptions are provided;

a) Povidone (PVP). Functional Category: Disintegrant, dissolution aid, suspending agent, tablet binder. p433

b) Hydroxypropylmethylcellulose (HPMC): Functional Category: coating agent, filmformer, rate-controlling polymer

for sustained release, stabilizing agent, suspending agent, tablet binder, viscosity-increasing agent. p252

c) Hydroxypropylcellulose (HPC): Functional Category: Coating agent, emulsifying agent, stabilizing agent, suspending agent, tablet binder, thickening agent, viscosity-increasing agent. p 244

d) Microcrystalline cellulose (MCC): Functional Category: Adsorbent, suspending agent, tablet and capsule diluent; tablet disintegrant. p102
[notice that tablet binder is not listed under Functional Category here];

THAT, copies of the above referred to pages from the Handbook of Drug Excipients, 3rd Ed, 2000, are attached to and made a part of this Declaration;

THAT, while there are cases and references where loose terminology might cause someone to label MCC as a binder because it does increase tablet bond, the properties of the MCC material did not lend it to actually being listed in Functional Category as a tablet binder in this key common reference for the pharmaceutical industry. Microcrystalline cellulose does not get very sticky/adhesive nor provide film former function when wetted, which a true binder does. In contrast, a regular binder not only increases tablet bond but more importantly and in addition when wetted provides a cohesive "glue" or film between materials which otherwise would not possess adequate adhesion or cohesion;

THAT, this same property of increasing adhesion or tackiness and film-formation when wetted of the polymeric binder defined in the above identified application serves the function of delaying precipitation of the rapidly precipitating drug. The delay of precipitation provided by MCC is inadequate for it to serve as binder in the tablet composition in the above identified application;

THAT, this inadequate delay of precipitation by MCC is borne out by the plot shown in Fig 1 which is attached;

THAT, Curve A shows the delay of precipitation profile of a soluble salt of a poorly soluble drug in the presence of hydroxy propyl methyl cellulose (HPMC);

THAT, Curve B shows the precipitation profile of a soluble salt of a poorly soluble drug in the absence of HPMC;

THAT, Curve C shows the precipitation profile of a soluble salt of a poorly soluble drug in the presence of MCC but no polymeric binder;

THAT, Curve C meets the definition of a rapidly precipitating drug as that term is defined in the above identified application (roughly 90% drug precipitates out of solution within 60 minutes to a less soluble form);

THAT, Curve C does not meet the requirement of delay of precipitation which is provided by the tablet composition claimed in the above identified application;

THAT, MCC is a separate and distinct component and is not a polymeric binder in the tablet composition of the above identified application.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 07 August 2003 Alice C. Martino

Alice C. Martino